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Title: Phase I Study of Topotecan, Ifosfamide, and Etoposide (TIME) with Autologous Stem Cell Transplant in Refractory Cancer: Pharmacokinetic and Pharmacodynamic Correlates

Running Title: High-dose TIME for chemorefractory malignancies

Key words: high-dose chemotherapy; non-Hodgkin lymphoma; topoisomerase I; topoisomerase II; topoisomerase inhibitors

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STATEMENT OF TRANSLATIONAL RESEARCH

Preclinical and in vivo data support sequencing antitumor agents as alkylating agent → topoisomerase I inhibitor → topoisomerase II inhibitor. This paradigm was the basis for this phase I high-dose chemotherapy regimen in relapsed/refractory malignancies amenable to autologous stem cell transplantation. The topoisomerase I inhibitor topotecan given intravenously was dose escalated to a maximum tolerated dose of 64 mg/m² given over three days (21.3 mg/m²/day). Mucositis was the dose-limiting toxicity and correlated with topotecan pharmacokinetics. Topoisomerase I levels in peripheral blood mononuclear cells correlated with overall and progression-free survival in univariate and multivariate analyses; higher levels predicted better survival. Our results demonstrate that topotecan in combination with high-dose etoposide (topoisomerase II inhibitor) and ifosfamide is tolerable, resulting in a response rate of 31% in the phase I part of this trial and 29% in the expanded cohort of lymphoma patients and 5-year overall survival rates of 18% and 25%, respectively.
ABSTRACT

Purpose: To determine the maximum tolerated dose (MTD) of topotecan in combination with ifosfamide, mesna, and etoposide (TIME), followed by autologous hematopoietic cell transplant (HCT), in patients with chemotherapy-refractory malignancies.

Experimental Design: Patients were treated with (in mg/m²/day) ifosfamide 3,333, mesna 3,333, and topotecan 3.3-28.3 during days -8 through -6 and etoposide 500 (days -5 through -3) followed by HCT on day 0. Once MTD was defined, we expanded this dosing cohort to include patients with high-risk lymphoma, due to activity seen during dose escalation. Topotecan pharmacokinetic analyses were performed, and topoiso merase I levels and activity were measured.

Results: The topotecan MTD in this regimen was 64 mg/m² (21.3 mg/m²/day). Mucositis was dose-limiting and correlated with topotecan dose level and area under the curve (AUC). Dose level was also correlated with length of hospitalization, number of days of parenteral nutrition, and neutrophil and platelet engraftment. Topotecan AUC was significantly correlated with time to platelet recovery. The baseline peripheral blood mononuclear cell topoiso merase I level was found to be a significant positive predictor for overall and progression-free survival. Topotecan AUC was positively correlated with dose level, with a trend toward decreasing clearance with increasing dose.

Conclusion: Topotecan can be a useful drug in the high-dose setting given its activity in some malignancies when given in standard dose. Pharmacokinetic monitoring may be a valuable tool for optimizing the use of topotecan and to avoid toxicity seen with high-systemic exposures. Baseline topoiso merase I levels may have an important role in predicting topotecan efficacy.
INTRODUCTION

High-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) is used in the treatment of a wide variety of relapsed and refractory malignancies. Despite the many reports of positive outcomes of HCT, patients continue to relapse posttransplant. One strategy to reduce posttransplant relapse is the development of novel conditioning regimens that take advantage of synergistic mechanisms of cytotoxicity. Most high-dose chemotherapy regimens include at least one alkylating agent because of the steep dose-response curves exhibited by these agents and because the dose-limiting toxicity in the standard dose setting is myelosuppression, allowing dose escalation in the HCT setting. Other drugs have been added to alkylating agents due to complementary mechanisms of cytotoxicity. Studies in several human cell lines and xenografts have shown that inhibition of DNA repair by a topoisomerase I (topo I) inhibitor may potentiate cytotoxicity induced by an alkylating agent (1-5). In addition, the sequential treatment with a topo I inhibitor followed by a topo II inhibitor has resulted in synergistic cytotoxicity (6, 7). These preclinical and in vivo data suggest a paradigm for sequencing these antitumor agents: an alkylating agent followed by a topo I inhibitor and then a topo II inhibitor. This specific sequence serves as the basis for the design of this trial.

In this phase I study, our aim was to define the dose-limiting toxicity of topotecan in combination with ifosfamide and etoposide. Our starting dose of topotecan was approximately 60% of the maximum tolerated dose (MTD) reported in standard dose phase I trials using an every 3- to 4-week administration schedule. The doses of ifosfamide and etoposide were 50% of the MTD determined in a previous dose escalation study done at our
institution (8). Due to activity seen during the present topotecan dose escalation study, we expanded the MTD cohort to include 16 patients with high-risk lymphoma. Preliminary clinical results have been previously described (9-11), and the mature and correlative data are presented here.

PATIENTS AND METHODS

Patients

Patients 18 to 64 years of age with histologically confirmed cancer and an Eastern Cooperative Oncology Group performance status of <2 were eligible. Patients were required to have adequate organ function and to have had no prior treatment with topotecan. Patients who had active infections, major metabolic disease (e.g., insulin-dependent diabetes or uncompensated adrenal or thyroid dysfunction), a positive antibody test for HIV, or leptomeningeal involvement were not eligible. All patients provided written informed consent. The research was reviewed and approved by the University of South Florida Institutional Review Board.

Patients with breast cancer were required to have metastatic disease that had failed to respond to an anthracycline-containing regimen and 1 other salvage regimen. Patients with intermediate or high-grade non-Hodgkin lymphoma (NHL) who had relapsed and failed to respond to >2 salvage chemotherapy regimens or had failed to achieve a complete remission after first-line induction chemotherapy and failed to respond to >1 salvage regimen were eligible. Patients with Hodgkin lymphoma were eligible if they had failed at least 3
chemotherapy regimens. Patients with other malignancies were considered if they had failed standard therapy for their disease.

Patients who were <55 years of age were eligible for the expanded MTD cohort if they had 1) intermediate or high-grade NHL and if they had relapsed and/or failed to respond to at least 2 chemotherapy regimens or had failed to achieve a complete remission after first-line induction chemotherapy and failed to respond to $\geq$1 salvage regimen; or 2) low-grade or indolent histologies and had relapsed or failed to achieve a complete remission after first-line induction chemotherapy and had failed to respond to $>2$ salvage chemotherapy regimens; or 3) had Hodgkin lymphoma and had received $\geq$2 salvage regimens. Patients who were $\geq$55 years of age were eligible if they had NHL with any histology or Hodgkin lymphoma if they had relapsed and/or failed to achieve a complete remission after first-line induction chemotherapy.

**Treatment Plan**

**Autologous Hematopoietic Cell Collection and Reinfusion**

Hematopoietic cells were mobilized, harvested, and transplanted per standard operating procedures of the Moffitt Cancer Center Stem Cell Processing Laboratory. Most patients received standard-dose chemotherapy followed by granulocyte colony-stimulating factor (G-CSF) for the purposes of tumor cyto reduction and mobilization of hematopoietic cells. Mobilizing regimens consisted of either cyclophosphamide, paclitaxel and G-CSF (patients with breast or ovarian cancer) or cyclophosphamide, etoposide and G-CSF (lymphoma...
patients). Patients who did not require further cytoreduction or in whom further chemotherapy was not appropriate received G-CSF alone.

**Conditioning Regimen**

Patients were treated with ifosfamide 3,333 mg/m²/day via a 2-hour intravenous (IV) infusion on days -8 through -6 followed immediately by topotecan 3.3 to 28.3 mg/m²/day (10-85 mg/m² total over 3 days) via a 30-minute IV infusion on days -8 through -6. Mesna dosing was 1,111 mg/m² via 30-minute IV infusion 30 minutes before and 4 and 8 hours after ifosfamide on days -8 through -6. Etoposide 500 mg/m²/day was given by IV infusion over 24 hours on days -5 through -3 beginning exactly 24 hours after the completion of the last topotecan infusion. Patients underwent HCT 48 hours after infusion of the chemotherapy regimen was completed (day 0).

Topotecan was dose escalated in cohorts of at least 4 patients each; patients were evaluated for 30 days posttransplant for toxicity. If, at a given dose level, 3 of 4 patients developed severe nonhematologic toxicities (with the exception of mucositis or enteritis), no further dose escalation and no further accrual at this level were allowed. Six more patients were entered at the preceding dose level to establish safety. If, at a given dose level, 1 or 2 of 4 patients developed severe toxicities, then 4 more patients were entered at that dose level. Only if 1 or 2 of 8 patients reported severe toxicity was the dose escalated further. If 5 or 6 of 8 patients experienced severe toxicity, then 6 more patients were entered at the previous dose level. Finally, if severe toxicity was observed in 3 or 4 of 8 patients, then 4 more patients were entered at this dose level for a total of 12 patients at that level. Patients could be treated at
lower dose levels that had been declared to be “safe” while accrual was halted at a higher
dose level until toxicity was evaluated. The MTD was defined as the dose level immediately
preceding that which caused severe toxicity in greater than 50% of patients. Severe toxicity
was defined as any grade 3 or 4 toxicity based on a toxicity scale adapted for bone marrow
transplant patients from the World Health Organization and the Eastern Cooperative
Oncology Group (see Table S1 in Supplementary Material).

Supportive Care

All patients received G-CSF 5 µg/kg/day beginning the day after transplant until an absolute
neutrophil count (ANC) of >10 × 10⁹ cells/L was achieved. Prophylactic antibiotics included
an oral quinolone, fluconazole, and, in patients with elevated herpes simplex virus titers,
acyclovir. Lymphoma patients also received prophylactic therapy for Pneumocystitis
pneumonia.

Safety Assessment

Routine laboratory evaluations included complete blood count, metabolic panels, and
renal/hepatic function tests, which were performed after the conditioning regimen was
started. The frequency and duration of tests were at the discretion of the treating physician
and based on the clinical status of each patient. Patients were monitored for adverse events
at least weekly until discharged posttransplant and during each clinic visit thereafter through
day 90 posttransplant.
Tumor Response

Response was assessed at 30 days, at 90 days, and at 1 year and then yearly post-HCT. A complete response (CR) was defined as no evidence of disease on physical examination, X-rays, or computed tomography scans for a minimum of 4 weeks. In patients with bone metastasis as their only evaluable disease, a CR was defined as recalcification of osteolytic lesions or complete resolution of bone scan abnormalities. A partial response (PR) was defined as a ≥50% decrease in the sum of the products of the diameters of all measurable lesions for ≥1 month with no concomitant appearance of new lesions for a minimum of 4 weeks. Stable disease (SD) was defined as a <50% decrease in measurable lesions without appearance of new lesions. Progressive disease was defined as a ≥25% increase in preexisting tumor or appearance of any new lesions.

For patients with nonmeasurable disease, responses were defined as follows: a CR was normalization of carcinoembryonic antigen (CEA) and/or cancer antigen 15-3 (CA 15-3) without the appearance of measurable tumor, a PR was a ≥50% decrease in CEA and/or CA 15-3, and SD was a <50% decrease in CEA and/or CA 15-3. Progressive disease was defined as an increase in CEA or CA 15-3 in patients with stable bone scans.

Topotecan Pharmacokinetics

Pharmacokinetic parameters were calculated by model-independent methods using WinNonlin software. For the phase I portion of the study, blood samples (4 mL) were collected at 15 minutes prior to the first and third topotecan infusions and 20, 35, 45, 60, and 90 minutes and 2.5, 4.5, 8.5, 12.5, 18.5, and 24.5 hours after the initiation of first and third
topotecan infusion. Patients in the expanded MTD cohort had samples drawn 30 minutes before and then at the end of the first infusion and then 15 minutes and 6 hours after the end of the infusion (12). Blood samples drawn from a lumen of the in-dwelling central venous catheter not being used for topotecan infusion were immediately centrifuged, with plasma separated, placed in a heparinized tube, and immediately frozen at –80°C. Ice-cold methanol was added to stop the closed ring (lactone) from opening. Plasma concentrations of both total topotecan and the closed lactone ring of topotecan were measured by high-pressure liquid chromatography (13, 14).

**Topo I Activity and Levels (Phase I Patients Only)**

**Band Depletion Assay for Topo I Activity**

Cleavable complex formation was used to assess topo I activity, which we analyzed as previously described with few modifications (15, 16). Details of these methods can be found in the Supplementary Material. Values reported are concentrations of topotecan required to induce DNA-topo I complexes such that 50% of the topo I could not enter a 10% polyacrylamide gel.

**Peripheral Blood Processing for Topo I Levels**

Thirty-five milliliters of whole blood were collected in tubes containing sodium citrate immediately before the start of the topotecan infusion. Blood was also collected at 35 minutes and 45 minutes and at 1, 1.5, 2.5, 4.5, 8.5, and 24 hours after the start of the 30-minute infusion and kept on ice throughout the procedure. These samples were collected on day -8.
and day –6 of high-dose chemotherapy. Details of the subsequent analyses can be found in the Supplementary Material.

**Statistical Analysis**

Response rates were reported with 95% confidence intervals by the Clopper-Pearson method. The Spearman correlation coefficient was utilized to estimate correlation between continuous variables. The Kaplan-Meier method was used to estimate overall survival and progression-free survival (PFS) from time of initiation of the treatment. PFS was defined by the absence of progression or death. The potential predictor variables were evaluated by the Cox proportional hazard model, using univariate and multivariate analysis with backward elimination method with $P$ out value of 0.15. Band depletion was not involved in the multivariate analysis because of missing observations for all patients in dose level 1. The Cox proportional hazard model was also used to evaluate the effects of pharmacokinetic variables on time to recovery of platelets or neutrophils. The cumulative incidence of transplant-related mortality was estimated by the Gray method (17); death and progression were considered event and competing risk, respectively.

**RESULTS**

Patients were enrolled between 9/1996 and 10/2002. Patient demographics and hematopoietic cell collection data are shown in Table 1. The majority of patients in the phase I study had refractory metastatic breast cancer. Of the eight NHL patients, two with low-grade/indolent histologies were transplanted in chemosensitive relapse (second or greater); the remaining NHL patients all had chemoresistant disease. Of the 11 patients with
intermediate grade or aggressive NHL in the expanded MTD cohort, 8 patients had diffuse large B cell histology and 1 patient each had angioimmunoblastic T cell lymphoma, anaplastic large cell lymphoma, and mantle cell lymphoma. Six patients had failed primary induction therapy, and 5 had relapsed disease. Of the three patients in the expanded MTD cohort who had low-grade/follicular histologies, one had chemosensitive disease and two had refractory disease. Both patients with Hodgkin lymphoma had failed primary induction therapy. The majority of patients received peripheral blood hematopoietic cells. Two patients received both bone marrow and peripheral blood-derived cells as they had inadequate collections from peripheral blood alone.

Table 2 shows grade 3/4 toxicity per topotecan dose level. Although initially not recognized as a potential dose-limiting toxicity, the severity and duration of grade 4 mucositis at dose level 8 (85 mg/m² over 3 days) were felt to be unacceptable, especially given the lack of improvement in efficacy seen at this level; further dose escalation was not undertaken and the MTD was dose level 7 (64 mg/m² over 3 days). Other grade 3 or 4 toxicities were randomly observed across all dose levels. The cumulative incidence of transplant-related mortality for all phase I patients at 100 days was 4%. Both deaths were a result of infectious complications. The length of hospitalization (from day of transplant to day of discharge), days of total parenteral nutrition (TPN), and median time to hematologic recovery by dose level are presented in Figure 1. The dose level of topotecan was significantly correlated with days of grade 4 mucositis (Spearman correlation coefficient = 0.53, \( P = 0.0002 \)), length of hospitalization (Spearman correlation coefficient = 0.51, \( P = 0.0004 \)), and the number of days patients received TPN (Spearman correlation coefficient = 0.44, \( P = 0.0032 \)). Engraftment of
neutrophils and platelets was also significantly correlated with topotecan dose level (hazard ratio = 0.51, \( P < 0.001 \) and hazard ratio = 0.96, \( P = 0.03 \), respectively).

Patients in the expanded MTD cohort had a nonhematologic toxicity profile similar to that seen in patients in the phase I study. The cumulative incidence of transplant-related mortality in the expanded cohort was 13%. One patient died 21 days after transplant as a result of hypokalemia-induced ventricular fibrillation resulting in myocardial infarction; another patient expired on day 11 after transplant of gram-negative bacterial sepsis. The median length of time patients received TPN was 12 days (6-24 days). The median time to hematologic recovery (engraftment) was 11 days (range, 10 to 13 days) for ANC >500/µL and 17 days (range, 12 to 32 days) for platelets >50,000/µL.

**Efficacy**

The overall response rate in the phase I study was 31%, with 5 CR (11%; 3 patients with breast cancer and 2 with NHL) and 9 PR (20%; 6 patients with breast cancer, 2 with NHL, 1 with ovarian cancer). An additional 17 patients had SD (39%). Responses did not appear to correlate with dose level: 2 CRs were seen at dose level 3 (20 mg/m² over 3 days) and 1 each occurred at dose levels 4, 5, and 7 (27 mg/m², 36 mg/m², and 64 mg/m², respectively, over 3 days). For patients on the phase I trial, overall survival at 1, 3, 5, and 10 years was 56%, 38%, 18%, and 11%, respectively; PFS at 1, 3, 5, and 7 years was shown to be 22%, 13%, 9%, and 4%, respectively (Figure 2A). At present, 5 patients are alive greater than 6 years after transplant (2 progression-free); 3 of these 5 patients have survived greater than 10 years. Three of the survivors had NHL (low grade), and two had chemorefractory metastatic breast cancer; 1 patient of each diagnosis is progression-free. Four of these long-
term survivors were treated at dose levels 1-3, and one was treated at dose level 7. There was a significant difference in overall survival between diagnoses (breast cancer vs. NHL vs. other; \( P = 0.009 \); Figure 2B and 2C). By Cox proportional hazards modeling, both breast cancer and NHL patients had significantly improved survival compared with patients who had other diagnoses.

Results of univariate and multivariate analyses for overall survival and PFS are shown in Table 3. Baseline topo I levels, topotecan (total) area under the curve (AUC), diagnosis, and age were significant predictors in the univariate analysis of overall survival. In the multivariate analysis, baseline topo I levels and diagnosis remained the only significant predictors, with increasing topo I levels correlating with increased overall survival and breast cancer patients having better survival than those being transplanted with diagnosis other than breast cancer or NHL. When PFS was the outcome, baseline topo I, age, and diagnosis were significant in the univariate analysis, but only topo I levels in peripheral blood mononuclear cells (PBMCs) appeared to be important in the multivariate analysis.

Fourteen patients in the expanded MTD cohort were evaluable for response (2 patients died before disease reevaluation post-transplant). The overall response rate was 29%, with 4 CR (29%); there were no PR. One additional patient achieved SD (7%). The 1-year, 2-year, 5-year, and 9-year PFS rates were 19%, 13%, and 6%, respectively; the 1-year, 2-year, 5-year, and 10-year overall survival rates were 44%, 25%, 25%, and 19% respectively. Three patients remain alive 10 years post-transplant; one has been progression free since transplant.
Pharmacokinetics

The pharmacokinetic parameters for topotecan (lactone and total concentrations) are summarized in Table 4. There were no significant differences between day -8 and day -6 parameters or between phase I and expanded MTD cohort patients; thus only day -8 results for phase I patients are shown. Maximum concentrations (Cmax) and AUC of topotecan (total) were positively correlated with dose level ($r = 0.9$ and $0.93$, respectively, with both $P < 0.0001$). Clearance appeared to decrease with increasing dose level ($r = -0.32; P = 0.04$); however, this could have been due to lower variability in clearance at higher dose levels as there was substantial variability in clearance at the lower dose levels, most likely caused by concentrations that were below quantifiable limits of the assay. Therefore, the clinical significance of this finding is questionable. Similar relationships were seen for the lactone assays. Higher total topotecan AUCs were associated with increasing duration of grade 4 mucositis; time to platelet recovery was also longer in patients with higher AUCs. No correlation was found between any of the pharmacokinetic parameters and maximum reduction in topo I levels, as measured by the band depletion assay.

Topo I Activity and Levels

Thirty-five patients on the phase I study had band depletion assays performed before the start of their conditioning regimen. The median value for all patients was 4.23 $\mu$M (range 1.7-40 $\mu$M). Lower values of this variable indicate that lower concentrations of topotecan were required to stabilize cleavable complexes and thus induce cytotoxicity. To evaluate the results of the assay, we calculated the ratio of topotecan Cmax to the band depletion assay...
results, postulating that the higher the ratio, the more likely topotecan levels would be over
the amount required to have a cytotoxic effect. Indeed, this ratio was found to be significantly
correlated with the duration of grade 4 mucositis (Spearman correlation coefficient = 0.41; \( P = 0.016 \)). There was no correlation between this ratio and PFS (hazard ratio = 2.99; 95% confidence interval: 0.35-25.61; \( P = 0.32 \)).

Baseline concentrations of topo I were measured in PBMCs of 34 phase I study patients (in arbitrary units: median 20,748; range 5230-49,937). These concentrations were not significantly correlated with days of grade 4 mucositis or time to recovery of platelets or neutrophils. Topo I concentrations were also measured over time after the administration of topotecan. The maximum reduction in topo I levels did not appear to be correlated with either maximum concentrations or AUC of topotecan. We did not evaluate reduction in topo I levels as a function of time above a particular topotecan level.

DISCUSSION

Several other phase I/II trials have evaluated topotecan in combination with other cytotoxic agents as conditioning therapy followed by autologous HCT. Schilder et al treated 20 patients who had chemo-naïve solid tumors with three or four cycles of paclitaxel (250 mg/m\(^2\) over 24 hours), carboplatin (AUC 16), and topotecan (10-15 mg/m\(^2\) over 24 hours) supported by peripheral blood hematopoietic cells and G-CSF (18). Dose-limiting toxicities were hemorrhagic stomatitis and prolonged hematopoietic recovery. Median days to neutrophil and platelet recovery were similar to those seen in our study. The MTD of topotecan when given in 3 cycles was 12.5 mg/m\(^2\); four cycles could be given when topotecan was dosed at 10
mg/m². Topotecan pharmacokinetics were linear over the dose range tested. Stomatitis was highly correlated with topotecan AUC ($P = 0.005$); 10 of 12 patients who developed grade 4 stomatitis had topotecan AUC of >1000 ng*hour/mL.

Three reports have been published by an M.D. Anderson group headed by Donato; this group evaluated the use of high-dose topotecan, melphalan, and cyclophosphamide as conditioning therapy before HCT in the treatment of ovarian cancer and multiple myeloma. In the first report, 53 patients were treated with topotecan (1.25 to 4 mg/m²/day from days -6 to -2), cyclophosphamide (1 g/m²/day on days -6 to -4), and melphalan (70 mg/m²/day on days -3 to -2) (19). The dose selected for further testing was 4 mg/m²/day for 5 days. Toxicity was limited to mucositis and diarrhea. In the second report, 18 patients with multiple myeloma were treated with the same regimen except the dosing for topotecan was 3-3.5 mg/m²/day (20). Similarly, the toxicity was limited to mucositis and diarrhea. This series was recently updated to include 60 myeloma patients using 3.5 mg/m²/day for five days (21). The most common non-hematological grade 3 and 4 toxicity was mucositis/stomatitis (22% of patients). Response rates and survival were comparable to local historical controls treated with high dose melphalan as a single agent prior to HCT.

Lotz et al evaluated escalating doses of single-agent topotecan using hematopoietic cell support. Topotecan was given at doses of 4-10 mg/m²/day for 5 days. Forty-nine patients were treated. Dose-limiting toxicity was diarrhea, and the MTD was determined to be 9.5 mg/m²/day x 5 days. A linear relationship between dose and AUC was observed (22). Litzow and colleagues from the Mayo Clinic dose escalated topotecan in combination with
cyclophosphamide (1.5 g/m²/day) and carboplatin (200 mg/m²/day) all as 4-day continuous infusions prior to HCT in 16 patients with relapsed or persistent ovarian or primary peritoneal carcinoma (23). The initial dose of topotecan was 1.5 mg/m²/day for 4 days with subsequent escalation to 6 mg/m²/day. Pretreatment biopsies were analyzed for topo I by immunohistochemistry, and topotecan pharmacokinetics were also evaluated. The dose-limiting toxicity was severe stomatitis requiring parenteral nutrition and narcotic administration; this was seen at 6 mg/m²/day. These authors defined the MTD as 4.5 mg/m²/day. Median topotecan clearance was 184 ml/min/m², which was very similar to the values reported in our evaluation. Also in concordance with our study was the finding that patients with tumors demonstrating weak or undetectable topo I had a shorter median time to progression than patients with tumors having readily detectable topo I staining.

Single-agent topotecan was used in the second of three cycles of high-dose therapy followed by hematopoietic cell support in women with advanced ovarian cancer (24). The starting dose of topotecan was 5 mg/m² given as a 72-hour continuous infusion starting on day -8. The largest dose given was 11 mg/m², but the authors stated that the MTD was not reached. Grade 3 or 4 nonhematologic toxicity included mucositis and increased amylase. Steady-state topotecan levels were similar for the 5 and 7 mg/m² doses. However, greater increases in steady-state levels were detected for the 9 and 11 mg/m² dose levels, consistent with reports of nonlinear pharmacokinetics with high doses of topotecan administered by continuous infusion. The terminal half-life of total topotecan following the end of the 72-hour infusion ranged from 1.8 to 4.7 hours.
We determined the maximally tolerated dose of topotecan to be 64 mg/m² when given over 3 days in combination with ifosfamide and etoposide in the treatment of refractory and heavily pretreated patients undergoing autologous HCT. This is higher than previous reports of topotecan given in this setting. The ability to dose-escalate to this level may have been due to a variety of factors: greater threshold for mucositis as a dose-limiting toxicity, use in a different combination of chemotherapy agents, or difference in scheduling. As seen with other studies, gastrointestinal toxicity was dose limiting, and, in our study, the duration of grade 4 mucositis was significantly correlated with dose level of topotecan as were the number of days that TPN was administered and length of hospitalization. We were also able to show that engraftment of neutrophils and platelets was correlated with dose level; these correlations have not been previously reported in the high-dose setting, although others have demonstrated similar correlations in the nontransplant setting (25, 26).

Others have shown a relationship between topotecan AUC and toxicity (18); our data also show that higher AUCs are associated with longer duration of severe mucositis as well as time to platelet recovery. Topotecan AUC appeared to be a significant negative predictor of overall survival in the univariate analysis. However, this effect was attenuated in the multivariate analysis. One explanation for this unexpected finding could be that patients having higher exposures to topotecan could have suffered subclinical toxicities, which would have prohibited effective therapy for posttransplant relapse, especially in this group of relatively heavily pretreated patients. Inability to receive salvage therapy would have affected overall survival, as the majority of these patients relapsed after transplant. Alternatively, this finding could have been an artifact of an unequal distribution of diagnoses across dose levels.
as diagnosis was a significant covariate in the multivariate analysis. We saw no benefit with respect to response rate or PFS with increasing topotecan AUC. A definitive dose-response relationship could not be established due to lack of power in this phase I trial. The recommended phase II dose is 64 mg/m² topotecan. Consideration could be given to adding palifermin to attenuate mucositis.

The other significant predictor of overall survival (and the only independent predictor for PFS) was baseline topo I levels, suggesting that higher levels of the pharmacologic target of topotecan enhanced sensitivity. This observation should be viewed with caution, however, as topo I levels in our study were measured in PBMCs. Whether baseline topo I in cancer cells would also be predictive is only speculative based on our results. Litzow and colleagues were able to show an association between topo I expression in pretreatment biopsies and time to progression (23), whereas others have failed to show a correlation between higher topo I levels and clinical response (27). Baseline topo I levels were not associated with indicators of toxicity. However, we did see a correlation between toxicity and the ratio of maximum topotecan levels and results of the band depletion assay.

During the phase I portion of the trial, we observed potential activity of this regimen in lymphoma patients and treated an expanded cohort of 16 patients at the MTD. We saw similar toxicity as that seen in the phase I study. The complete response rate in this refractory disease population was 29% with a 2-year progression-free survival of 13%. Because the regimen did not appear to be superior to currently used regimens with respect to toxicity or efficacy, further study of the regimen was not pursued.
Extensive work has been done by investigators at St. Jude’s Children’s Research Hospital using pharmacokinetic modeling to develop more effective scheduling of topotecan in the standard dose setting (28, 29). Their findings have shown that pharmacokinetically targeting topotecan is feasible and may lead to improved response rates in children with neuroblastoma. This same approach should be studied when topotecan is used in the high-dose setting due to the variability of topotecan exposure and increased likelihood of toxicity at higher systemic exposures. In addition, baseline topo I levels may have an important role in predicting the efficacy of topotecan and should be explored further. To this end, our transplant program is conducting a clinical trial of high-dose topotecan in combination with melphalan in the HCT setting for treatment of myeloma. Both topotecan pharmacokinetics and topo I levels are being evaluated with the aim of corroborating the findings of the TIME study.
ACKNOWLEDGMENTS

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Table 1. Patient Demographics and Hematopoietic Cell Collections

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase I (n = 45)</th>
<th>Expanded MTD Cohort (n = 16)</th>
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<tr>
<td>Primary tumor type, patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>29 (64)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8 (18)</td>
<td>14 (88)</td>
</tr>
<tr>
<td>Low grade/indolent</td>
<td>4 (9)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Intermediate grade/aggressive</td>
<td>4 (9)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>7 (16)</td>
<td></td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic cell source, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow (no priming)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide/Taxol/G-CSF</td>
<td>33 (73)</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide/Etoposide/G-CSF</td>
<td>7 (16)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>G-CSF</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide/Taxol/G-CSF (PB)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>G-CSF + GM-CSF (PB)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>CD34+ cells/kg collected, x 10^6; median (range)</td>
<td>4.01 (0.11-72.10)</td>
<td>3.01 (2.05-8.48)</td>
</tr>
</tbody>
</table>

Abbreviations: MTD, maximum tolerated dose; PB, peripheral blood.
Table 2. Number of Patients with Grade 3 or 4 Nonhematologic Toxicities per Topotecan Dose Level

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>1 mg/m² (n=4)</th>
<th>2 mg/m² (n=6)</th>
<th>3 mg/m² (n=4)</th>
<th>4 mg/m² (n=5)</th>
<th>5 mg/m² (n=9)</th>
<th>6 mg/m² (n=5)</th>
<th>7 mg/m² (n=7)</th>
<th>8 mg/m² (n=5)</th>
<th>Expanded MTD Cohort (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>1 (25%)</td>
<td>2 (33%)</td>
<td>2 (50%)</td>
<td>4 (80%)</td>
<td>5 (56%)</td>
<td>5 (100%)</td>
<td>7 (100%)</td>
<td>4 (80%)</td>
<td>15 (94%)</td>
</tr>
<tr>
<td>No. of days with grade 4 mucositis, Median (range)</td>
<td>0 (0-1)</td>
<td>0 (0-10)</td>
<td>2.5 (0-6)</td>
<td>2 (0-7)</td>
<td>1 (0-20)</td>
<td>5 (1-9)</td>
<td>6 (4-11)</td>
<td>8 (0-12)</td>
<td>6 (0-20)</td>
</tr>
<tr>
<td>Enteritis</td>
<td>0 (17%)</td>
<td>1 (75%)</td>
<td>3 (60%)</td>
<td>3 (44%)</td>
<td>4 (40%)</td>
<td>2 (57%)</td>
<td>3 (60%)</td>
<td>5 (31%)</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>0 (17%)</td>
<td>1 (25%)</td>
<td>1 (20%)</td>
<td>0 (11%)</td>
<td>0 (14%)</td>
<td>1 (20%)</td>
<td>0 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical function</td>
<td>0 (17%)</td>
<td>1 (17%)</td>
<td>0 (20%)</td>
<td>1 (20%)</td>
<td>1 (14%)</td>
<td>0 (14%)</td>
<td>0 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve function</td>
<td>0 (17%)</td>
<td>1 (17%)</td>
<td>0 (20%)</td>
<td>0 (20%)</td>
<td>0 (14%)</td>
<td>1 (20%)</td>
<td>0 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in ejection fraction</td>
<td>0 (17%)</td>
<td>1 (17%)</td>
<td>0 (20%)</td>
<td>1 (20%)</td>
<td>0 (14%)</td>
<td>1 (20%)</td>
<td>1 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary clinical status</td>
<td>1 (25%)</td>
<td>1 (17%)</td>
<td>0 (20%)</td>
<td>1 (14%)</td>
<td>0 (14%)</td>
<td>1 (20%)</td>
<td>1 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrelapse deaths</td>
<td>0 (14%)</td>
<td>0 (14%)</td>
<td>0 (14%)</td>
<td>0 (14%)</td>
<td>0 (14%)</td>
<td>1 (20%)</td>
<td>1 (13%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

- Fungal infection
- Septic shock
- Arrhythmia (1) and bacterial sepsis (1)
Table 3. Results of Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P</td>
<td>Hazard Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topotecan AUC (total)</td>
<td>1.31 (1.08 – 1.59)</td>
<td>0.006</td>
<td>0.146</td>
<td></td>
</tr>
<tr>
<td>Band depletion (topo I activity)</td>
<td>0.98 (0.93 – 1.04)</td>
<td>0.501</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topo I levels</td>
<td>0.94 (0.89-0.98)</td>
<td>0.007</td>
<td>0.90 (0.86 - 0.95)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximum decrease in topo I levels</td>
<td>1.02 (1.00 – 1.04)</td>
<td>0.071</td>
<td>0.465</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.96 (0.92 – 0.99)</td>
<td>0.031</td>
<td>0.897</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0.30 (0.13 – 0.70)</td>
<td>0.006</td>
<td>0.19 (0.06 – 0.68)</td>
<td>0.009</td>
</tr>
<tr>
<td>NHL</td>
<td>0.23 (0.07 – 0.77)</td>
<td>0.017</td>
<td></td>
<td>0.388</td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topotecan AUC (total)</td>
<td>1.43 (0.95 – 2.15)</td>
<td>0.089</td>
<td>0.495</td>
<td></td>
</tr>
<tr>
<td>Band depletion (topo I activity)</td>
<td>0.99 (0.95 – 1.04)</td>
<td>0.799</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topo I levels</td>
<td>0.95 (0.91 - 0.99)</td>
<td>0.033</td>
<td>0.93 (0.89 – 0.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximum decrease in topo I levels</td>
<td>1.01 (0.99 – 1.03)</td>
<td>0.273</td>
<td>0.562</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.96 (0.92 – 1.00)</td>
<td>0.057</td>
<td>0.502</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0.38 (0.17 – 0.88)</td>
<td>0.024</td>
<td>0.253</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>0.44 (0.15 – 1.31)</td>
<td>0.140</td>
<td></td>
<td>0.154</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CI, confidence interval; NHL, non-Hodgkin lymphoma. **“Others” refers to diagnoses other than breast cancer. This group served as the reference group in the analyses (hazard ratio = 1).
<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Daily Dose Level, mg/m²</th>
<th>Cmax, µM (range)</th>
<th>T₁/₂, h (range)</th>
<th>Cl, L/h/m² (range)</th>
<th>V₅₀₀, L/m² (range)</th>
<th>AUC, µM • h (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n=4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>0.18 (0.14-0.26)</td>
<td>2.7 (1.7-5.1)</td>
<td>12.97 (11.50-21.67)</td>
<td>49.2 (31.1-72.4)</td>
<td>0.56 (0.33-0.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.18 (0.14-0.20)</td>
<td>2.6 (0.6-4.8)</td>
<td>27.95 (21.28-63.95)</td>
<td>56.6 (28.8-81.6)</td>
<td>0.26 (0.11-0.34)</td>
</tr>
<tr>
<td>2</td>
<td>n=6</td>
<td>0.21 (0.13-0.75)</td>
<td>3.0 (2.0-9.9)</td>
<td>15.44 (10.12-26.17)</td>
<td>41.19 (29.27-46.04)</td>
<td>0.65 (0.42-0.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.20 (0.09-0.68)</td>
<td>2.7 (1.5-5.1)</td>
<td>66.8 (33.8-118)</td>
<td>111 (39.6-183)</td>
<td>0.27 (0.24-0.37)</td>
</tr>
<tr>
<td>3</td>
<td>n=4</td>
<td>0.33 (0.25-0.43)</td>
<td>2.6 (2.0-3.4)</td>
<td>17.14 (9.32-21.50)</td>
<td>57.5 (43.1-74.5)</td>
<td>0.86 (0.68-1.57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.23 (0.15-0.43)</td>
<td>3.4 (2.0-8.9)</td>
<td>28.07 (28.07-49.01)</td>
<td>113 (81.9-302)</td>
<td>0.38 (0.30-0.52)</td>
</tr>
<tr>
<td>4</td>
<td>n=5</td>
<td>0.52 (0.34-1.1)</td>
<td>3.3 (2.9-4.2)</td>
<td>12.05 (10.14-23.96)</td>
<td>53.7 (39.1-79.7)</td>
<td>1.63 (0.82-1.93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.48 (0.34-0.89)</td>
<td>3.1 (2.6-4.0)</td>
<td>25.61 (25.61-46.73)</td>
<td>91.6 (67.9-120)</td>
<td>0.70 (0.42-0.77)</td>
</tr>
<tr>
<td>5</td>
<td>n=9</td>
<td>0.65 (0.42-1.21)</td>
<td>2.9 (1.7-10.7)</td>
<td>16.43 (5.85-20.45)</td>
<td>30.11 (18.06-40.77)</td>
<td>1.86 (1.28-4.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.61 (0.30-1.12)</td>
<td>3.2 (1.8-7.2)</td>
<td>31.41 (18.06-40.77)</td>
<td>94.4 (48.7-168)</td>
<td>0.88 (0.64-1.45)</td>
</tr>
<tr>
<td>6</td>
<td>n=5</td>
<td>0.87 (0.84-1.47)</td>
<td>3.1 (2.3-4.1)</td>
<td>12.62 (9.61-16.90)</td>
<td>23.53 (20.38-34.04)</td>
<td>2.77 (2.07-3.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.80 (0.63-1.46)</td>
<td>3.3 (2.0-3.9)</td>
<td>48.1 (34.5-65.7)</td>
<td>76.6 (54.3-114)</td>
<td>1.48 (1.03-1.71)</td>
</tr>
<tr>
<td>7</td>
<td>n=7</td>
<td>1.08 (0.83-4.17)</td>
<td>2.6 (2.1-6.3)</td>
<td>13.43 (7.93-17.79)</td>
<td>29.10 (14.47-35.17)</td>
<td>3.47 (2.62-5.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.92 (0.57-4.06)</td>
<td>2.7 (1.9-7.0)</td>
<td>63.9 (36.2-98.1)</td>
<td>95.8 (48.4-199)</td>
<td>1.60 (1.32-3.22)</td>
</tr>
<tr>
<td>8</td>
<td>n=5</td>
<td>2.12 (1.32-3.03)</td>
<td>2.4 (2.0-5.8)</td>
<td>10.78 (6.20-12.34)</td>
<td>25.77 (20.39-27.85)</td>
<td>5.73 (5.02-9.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.67 (1.21-2.70)</td>
<td>2.3 (2.1-4.4)</td>
<td>41.1 (38.3-64.0)</td>
<td>81.5 (41.2-107)</td>
<td>2.40 (2.22-3.03)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; Cl, clearance; Cmax, maximal concentration; T₁/₂, half life; V₅₀₀, volume of distribution. Daily dose was given each day for 3 days.
FIGURE LEGENDS

Figure 1. Relationship between topotecan dose level and toxicity outcomes and engraftment for patients in the phase I trial. (A) Dose level versus days on total parenteral nutrition (TPN). (B) Dose level versus length of hospitalization. (C) Dose level versus days to ANC >500 cells/µL. (D) Dose level versus days to platelets >50,000 cells/µL. (E) Dose level versus number of days with grade 4 mucositis. The horizontal line in the middle of each box indicates the median, whereas the top and bottom of each box represents the 75th and 25th percentiles, respectively. The whiskers above and below the box represent the 90th and 10th percentile, respectively.

Figure 2. Overall survival and progression-free survival for patients in the phase I trial. (A) Overall survival and progression-free survival for all phase I patients. (B) Overall survival for phase I patients by disease type (breast, NHL, and other). (C) Progression-free survival for phase I patients by disease type (breast, NHL, and other).
FIGURE 1

A

B

C

D

E

Days on TPN

Length of Hospitalization (Days)

Days to ANC > 500 cells/μL

Days to Platelets > 50,000 cells/μL

No. of Days with Grade 4 Mucositis

Dose level (mg/m²)

Dose level (mg/m²)

Dose level (mg/m²)

Dose level (mg/m²)
FIGURE 2

A

Overall Survival
Progression-Free Survival
Censored

Median OS: 14.6 months (95% CI: 8.2 - 36.2)
Median PFS: 3.0 months (95% CI: 2.0 - 6.0)

No. at Risk
OS 45 25 17 17 10 8 6 5 4 3 3
PFS 45 10 6 6 4 4 3 1 1 0 0

B

Breast
NHL
Others
Censored

Median OS: 14.6 months (95% CI: 8.2 - 36.2)
Median PFS: 3.0 months (95% CI: 2.0 - 6.0)

No. at Risk
Breast 29 21 13 13 7 5 3 2 1 1 1
NHL 8 3 3 3 3 3 3 3 3 2 2
Others 8 1 1 1 1 0 0 0 0 0 0

C

Breast
NHL
Others
Censored

Median OS: 14.6 months (95% CI: 8.2 - 36.2)
Median PFS: 3.0 months (95% CI: 2.0 - 6.0)

No. at Risk
Breast 29 8 4 4 3 3 2 0 0
NHL 8 2 2 2 1 1 1 1 1
Others 8 0 0 0 0 0 0 0 0
A

Overall Survival
Progression-Free Survival
Censored

Median OS: 14.6 months (95% CI: 8.2 - 36.2)
Median PFS: 3.0 months (95% CI: 2.0 - 6.0)

B

Breast
NHL
Others
Censored

Median OS: 14.6 months (95% CI: 8.2 - 36.2)
Median PFS: 3.0 months (95% CI: 2.0 - 6.0)

C

Breast
NHL
Others
Censored

Median OS: 14.6 months (95% CI: 8.2 - 36.2)
Median PFS: 3.0 months (95% CI: 2.0 - 6.0)
Clinical Cancer Research

Phase I Study of Topotecan, Ifosfamide, and Etoposide (TIME) with Autologous Stem Cell Transplant in Refractory Cancer: Pharmacokinetic and Pharmacodynamic Correlates

Janelle B Perkins, Steven C. Goldstein, Jana L Dawson, et al.

*Clin Cancer Res* Published OnlineFirst October 25, 2011.

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